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MINI REVIEW

Cholestasis in the newborn and infant

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Summary Neonatal cholestasis occurs in approximately 1 in 2500 term infants, the most common underlying disease being biliary atresia, viral infections and α_1-antitrypsin deficiency. The incidence of cholestasis is much higher in extremely premature newborns. The etiology of biliary atresia remains unclear, which in turn makes the search for additional treatments to surgery challenging. Reliable non-invasive tools to differentiate biliary atresia from other forms of neonatal cholestasis need to be further investigated. Despite important findings in the last decades, the pathogenesis of cholestatic liver disease in α_1-antitrypsin deficiency remains to be clarified. Any such explanation would also need to explain why only a minority of individuals with PiZZ phenotype develop liver disease. For other genetic diseases causing neonatal cholestasis, such as Alagille's syndrome and progressive familial intrahepatic cholestasis the breakthrough within the field of molecular biology has definitely deepened our understanding of both etiology and pathogenesis. However, the correlation between genotype and phenotype is rarely obvious and for several patients with the seemingly correct phenotype no known genetic mutation is detected. A stepwise approach to the management of cholestasis in the newborn and infant is suggested, where percutaneous liver biopsy is of value to select patients with suspected biliary atresia for laparotomy.

Introduction

Decreased or obstructed bile flow at any level from the hepatocyte to the junction of the extrahepatic biliary tree and the duodenum is referred to as cholestasis. Generally, jaundice and pale stools are regarded as the main clinical signs of cholestasis. However, other phenomena such as dark urine, pruritus, unexplained profuse bleedings and steatorrhea could be cholestatic manifestations, as well. Biochemically, a conjugated hyperbilirubinemia and/or increased levels of gamma-glutamyl transpeptidase (G-GT), alkaline phosphatase (ALP) and fasting bile acids are noted.

Clinical presentation

Early after birth there is an immaturity in the enterohepatic circulation of bile acids, resulting in a state of physiologic

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cholestatis [1]. This may last for at least the first half year of life, and during this period there is an increased vulnerability to cholestatic agents. Neonatal cholestasis will most often present as prolonged jaundice, defined as visible icterus beyond 2 weeks of age. Such babies should always be investigated for conjugated hyperbilirubinemia and if this is detected further work-up for cholestasis is mandatory [2]. At the same time, prothrombin time must be checked and pathologic levels need to be treated with intravenous vitamin K, to avoid detrimental bleedings.

Causes

A large number of causes for neonatal cholestasis have been identified [3]. Somewhat simplified they are often classified as either extrahepatic or intrahepatic in origin. In the first group biliary atresia (BA) is by far the most common. The second group, which includes a long list of different diseases, can be referred to as intrahepatic neonatal cholestasis. The term neonatal hepatitis is often used for the latter group. However, while this could be an adequate term considering the histological picture, it should be avoided in the clinical setting because it might imply an infectious etiology, which is only one of several possible causes.

The most common causes of intrahepatic neonatal cholestasis include α_1-antitrypsin deficiency (AATD), viral infections and genetic cholestatic disorders, such as Alagille's syndrome and different types of progressive familial intrahepatic cholestasis (PFIC).

Despite important achievements in the last decades a certain percentage of newborns and infants with intrahepatic cholestasis remain without etiology. Although a proportion of such cases displays only transient cholestasis, further research efforts are needed to narrow this gap of knowledge (Table 1).

Incidence

The incidence of neonatal cholestasis is difficult to establish, since mostly referred patients are reported and this would underestimate the number of mild cases. However, the generally accepted figure is between 1 in 2500—5000 term infants [4]. For extremely premature babies this figure is much higher, due to the combination of several risk factors such as immaturity, lack of enteral feedings, long-term use of total parenteral nutrition, and frequent episodes of septicemia. In the subset of babies born before 28 weeks of gestation the incidence of cholestasis is thought to be increased by 100—200 times compared to term babies.

For BA, which is easier to define more strictly, the suggested incidence in different populations is 1 in 8000—20,000 infants [5,6].

Table 1 The most common causes for cholestasis in term infants, with estimated proportions of the total number.

Disease	Proportion of total (%)
Biliary atresia	30
Infections	15
α_1-antitrypsin deficiency	10
Alagille syndrome	5
PFIC types 1, 2, 3	5
Other rare inborn errors of metabolism	3
Chromosomal aberrations	2
Miscellaneous: endocrine deficiencies, cystic fibrosis, asphyxia, common bile duct lithiasis, neonatal sclerosing cholangitis	1
Idiopathic	30

Biliary atresia (BA)

BA is an obliteration of the hepatic or common bile duct at any point from the porta hepatis to the duodenum with an ongoing intrahepatic bile duct damage. It is a heterogenous disorder, with a subgroup of 10—20% presenting with associated anomalies of the heart, gastrointestinal tract and/or genito-urinary tract, i.e. syndromic variants [7].

The etiology of BA is unclear. Previous studies suggest either an alteration in the remodeling of the so-called ductal plate during the first trimester of fetal life, an association to different viral infections, immunological mechanisms, or alterations in the vascular system. Repeated cases in the same family are uncommon, and monozygotic twins are most often discordant for the disease.

Patients with BA most commonly present at the age of 2—6 weeks with jaundice and pale stools. Thus, primary care physicians at well baby clinics need to actively inspect the stools of babies with prolonged jaundice. Recent data from Taiwan suggest that population-based screening of all infants, by the use of stool color cards sent to the parents can speed up the detection of cases with BA, and in turn improve the success rate of the following surgical procedure [8].

To visualize the lack of biliary excretion to the gut in BA, hepatobiliary scintigraphy with technetium labeled iminodiacetic acid compounds, possibly enhanced by previous pharmacological choleretic treatment is used in some centers. However, the specificity of this method is very questionable, because patients with severe intrahepatic cholestasis will often lack excretion as well. A needle liver biopsy, on the other hand, if interpreted by an experienced pathologist, will show a histological pattern specific for BA in 90—95% of the true cases [2].

α_1-antitrypsin deficiency (AATD)

AAT deficient individuals are classified according to the protease inhibitor (Pi) type that is determined by agarose electrophoresis. The most common deficiency type, and the only one which results in neonatal cholestasis, is designated PiZZ. This yields an AAT level of 0.2—0.3 g/L, i.e. around 25% of normal levels. In a Swedish population-based study of 200,000 babies born in the mid-70s, Pi type ZZ was found in 1 in 1600 babies, of whom 10% had neonatal cholestasis [9]. The mechanism for the liver disease in AATD, and the reason why only a minority of deficient individuals with PiZZ will develop this is still unclear, but subject to intense research. The outcome for these patients is very variable.